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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/751,744	01/05/2004	Mark A. Schenerman	AE300US1	6583

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EXAMINER	
ZEMAN, ROBERT A	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/751,744	SCHENERMAN ET AL.	
	Examiner	Art Unit	
	ROBERT A. ZEMAN	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,8,9,19-26 and 43-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,8,9,19-26 and 43-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10-13-2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10-13-2008 has been entered.

The amendment and response filed on 10-13-2008 are acknowledged. Claim 1has been amended. Claims 1-2, 4, 8-9, 19-26 and 43-51 are pending and currently under examination.

Information Disclosure Statement

The Information Disclosure Statement filed on 10-13-2008 has been considered. An initialed copy is attached hereto.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description Rejection

Applicant is directed to the Guidelines for the Examination of Patent Applications under the 35 U.S.C. 112, first paragraph "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The rejection of claims 1-2, 4, 8-9, 19-26 and 43-51 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for essentially the reasons set forth in the previous Office action in the rejection of claims 1-9 and 19-26 is maintained for reasons of record. The claim(s) still contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant argues:

1. The specification would lead one of skill in the art to recognize that Applicant had possession of the claimed invention as evidenced by the disclosures at page 3, lines 25 to 33; page 6, lines 31-33; page 7, lines 3-5; page 17, lines 11-15; page 20; Table 6; and page 21, lines 20-24. The said disclosure represents a representative number of species of the claimed genus. Applicant's arguments have been fully considered and deemed non-persuasive.

In response to Point 1, the instant claims encompass any and all IgG molecules (not merely human) which can comprise up to 7 separate substitutions. The portions of the specification indicated by Applicant are extremely limited in scope and do not constitute a representative number of the claimed genus. For example:

- Page 3, lines 25 to 33, discloses only 2 specific mutants. Human IgG1 wherein H237 is substituted or G249 of the IgG1 CH2 domain is substituted.
- Page 6, lines 31-33 and page 7, lines 3-5, discloses a single mutant wherein S241 is substituted with proline in human IgG4.
- Page 17, lines 11-15, makes a generic statement about replacing a proline residue with a non-proline residue.
- Table 6 on page 20 discloses single or dual mutations in human gamma 1 and human gamma 4.
- Page 21, lines 20-24, discloses single mutants wherein G249 is substituted for in human IgG1.

Moreover, the specification is silent (with the exception of the specific examples set forth above) as to which amino acid residues can be substituted with which amino acid thereby conferring the claimed resistance to heat degradation. Additionally, the instant claims are drawn to modified IgG molecules but provide no baseline sequence for the "unmodified" IgG molecule. Moreover, the instant claims encompass non-human IgG but do not provide a baseline sequence for them. Additionally, the instant claims refer to the same Kabat position for all IgG subclasses though there is variation in the length of said sequences. Finally, the specification discloses only a small portion of the immunoglobulins encompassed by the instant claims and is limited to specific substitutions that can be made only when the recited residue is a specific amino acid. (i.e. when position 236 is a serine you can substitute with proline). There is no limitation in the instant claims as to what amino acid must be present at a given position. Consequently, since the

specification does not disclose a representative number of species of the claimed genus, the claimed genus is not properly described.

As outlined previously, the instant claims are drawn to modified IgG molecules comprising a modified hinge region comprising one or more amino acid substitutions at a position corresponding to positions 233-237 or 239 of human IgG and/or an amino acid modification at a residue corresponding to position 249 of a human IgG heavy chain wherein said modified IgG exhibits reduced degradation upon heating to 55°C for one week compared to an unmodified IgG and pharmaceutical compositions comprising said modified IgG molecules. The claims are drawn to a vast genus of modified immunoglobulins containing one or more substitutions to positions 233-237 or 238 of an undefined hinge region of a human IgG and/or a substitution at position 249 of a human IgG heavy chain wherein said substitutions confer a resistance to heat degradation. Consequently, since the instant claims recite specific "residues", it is deemed that the baseline IgG sequences constitute essential material. The MPEP states:

> **608.01(p)**
> Newly filed applications obviously failing to disclose an invention with the clarity required are discussed in MPEP § 702.01.A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which the invention pertains to make and use the invention as of its filing date. *In re Glass,* 492 F.2d 1228, 181 USPQ 31(CCPA 1974).
>
> An application as filed must be complete in itself in order to comply with 35 U.S.C. 112. Material nevertheless may be incorporated by reference, *Ex parte Schwarze*, 151 USPQ 426 (Bd. App. 1966). An application for a patent when filed may incorporate "essential material" by reference to (1) a U.S. patent, (2) a U.S. patent application publication, or (3) a pending U.S. application, subject to the conditions set forth below.
> "Essential material" is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112). In any application which is to issue as a U.S. patent, essential material **may not be** incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, **(2) non-patent publications**, (3) a U.S. patent or application which itself incorporates "essential material" by reference, or (4) a

foreign application.

To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably Convey to the skilled artisan that Applicant has **possession** of the claimed invention. To adequately describe the genus of the aforementioned modified immunoglobulins, Applicant must adequately describe the specific mutations that would lead to the desired increase in heat resistance. However, the specification does not disclose distinguishing and identifying features of a representative number of members of the genus of modified immunoglobulins to which the claims are drawn, such as a correlation between the structure of the immunoglobulin and its recited function (increased resistance to heat), so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus of immunogenic compositions. Moreover, the specification fails to disclose which amino acids replaced so that the resultant immunoglobulins possess the desired characteristics. The specification is equally silent with regard to which amino acids can be used in said substitution so that the resultant immunoglobulin possesses the desired characteristic. Therefore, since the specification fails to adequately describe at least a substantial number of mutations that would convey an increased resistance to degradation by heat, the specification fails to adequately describe at least a substantial number of members of the claimed genus of immunoglobulins possessing the desired characteristics.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show

that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome and form immunoglobulins. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining or altering a function are limited. Certain positions in the sequence are critical to the

three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of modified immunoglobulins, the skilled artisan •could not immediately recognize or distinguish members of the claimed genus of modified immunoglobulins with increased resistance to degradation by heat. Therefore, because the art is unpredictable, in accordance with the Guidelines, the description of mutations conferring increased resistance to heat degradation is not deemed representative of the genus of modified immunoglobulins to which the claims refer.

Enablement Rejection

The rejection of claims 1-2, 4, 8-9, 19-26 and 43-51 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for essentially the reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant argues:

1. The specification not only teaches which amino acid substitutions can be made in which Kabat positions in the hinge or heavy chain constant regions to achieve improved heat resistance, the specification also teaches how one can substitute such amino acids as well as test for improved stability. Consequently, the skilled artisan does not have to "guess" at which modifications need to be made in order to achieve claimed heat resistance.

Applicant's arguments have been fully considered and deemed non-persuasive.

In response to Point 1, the specification fails to disclose which amino acid residues can be substituted with which amino acid thereby conferring the claimed resistance to heat degradation as the instant claims refer to the same Kabat position for all IgG subclasses though there is variation in the length of said sequences. Moreover, the specification (e.g. Table 6 etc.) discloses only a small portion of the immunoglobulins encompassed by the instant claims Said table is limited to the substitutions that can be made only when the recited residue is a specific amino acid. (i.e. when position 236 is a serine you can substitute with proline). There is no limitation in the instant claims as to what amino acid must be present at a given position.

As outlined previously, The instant claims are drawn to modified IgG molecules comprising a modified hinge region comprising one or more amino acid substitutions at a position corresponding to positions 233-237 or 239 of human IgG and/or an amino acid modification at a residue corresponding to position 249 of a human IgG heavy chain wherein said modified IgG exhibits reduced degradation upon heating to 55°C for one week compared to an unmodified IgG and pharmaceutical compositions comprising said modified IgG molecules However, Applicant has failed to provide sequences on which the claimed substitutions are based. Consequently, the skilled artisan cannot make and use the claimed invention. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome and form immunoglobulins. Bowie et al. further teach that the

problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining or altering a function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306) Therefore, given the lack of sequences on which the claimed mutations are based, the lack of success in the art, the lack of working examples commensurate in scope to the claimed invention and the unpredictability of the effects of a given substitution, the specification, as filed, does not provide enablement for the claimed modified immunoglobulins.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT A. ZEMAN whose telephone number is (571)272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m. .

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on (571) 272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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/Robert A. Zeman/
Primary Examiner, Art Unit 1645
January 15, 2009